A double-blind, placebo-controlled study of topical tetracaine in the treatment of herpes labialis

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Background: Before the September 1996 approval of 1% penciclovir cream for the treatment of herpes labialis, no other prescription topical therapy was approved for the treatment of this recurrent viral disease affecting approximately 20% of the adult population of the United States. Local anesthetics, such as tetracaine, have been used in over-the-counter topical products, but are only labeled for the relief of pain and itching associated with cold sores and fever blisters.

Objective: The purpose of this study was to determine whether a topical preparation of a tetracaine cream is safe and effective in the treatment of recurrent herpes labialis in immunocompetent patients.

Methods: A double-blind, placebo-controlled study was conducted to assess the relative effectiveness and safety of 1.8% tetracaine equivalent in a cream base versus placebo in the treatment of herpes labialis in immunocompetent adults. In this study, patients applied medication up to 6 times daily until the lesions healed (scab loss), but for no more than 12 days. The patients were monitored on the day of enrollment, once during the course of treatment, and at a final visit after the lesions had healed. Patients assessed themselves the day of scab formation and the day the scab fell off. They also graded, on a daily basis, their perception of relief from itching and pain and the overall benefit.

Results: The results from 72 patients (35 = placebo; 37 = active) showed that scab formation occurred in a mean of 2.4 ± 0.27 days for the placebo group and 2.3 ± 0.26 days for the active group. Healing time (scab loss) occurred in a mean 7.2 ± 0.36 days for the placebo group and in 5.1 ± 0.35 days in the active group. The difference observed for healing time between the placebo and the active tetracaine cream was statistically significant (P = .0002). This represents an approximately 30% reduction in the healing time for the active group compared with the placebo group. In addition, the study patients ranked the benefit of their treatment on a daily basis and graded the overall benefit of the therapy at their final visit. The ranking was on a 1 to 10 index scale (1 = no benefit at all; 10 = very effective treatment). At the final visit there was a statistically significant difference in the benefit index for active preparation versus placebo for this subjective evaluation (placebo index, 5.9 ± 0.6; active index, 7.3 ± 0.48 [P = .0359]). The subjects also evaluated relief from itching and pain on a daily basis. Relief from itching was significantly greater in the active group than in the placebo group on days 2 and 3 after initiation of the treatment. Pain was not found to be severe in either the placebo or active treatment groups. At day 2 of treatment and beyond, pain scores never were greater than 3.2 ± 0.28 for active on a scale in which 1.0 represented “no pain at all” and 10 represented “most severe pain imaginable.” Although mean values for pain were always less for the active therapy, lesional pain scores never reached statistically significant lower values for active compared with placebo.

Conclusion: Our findings indicate that a 1.8% topical tetracaine cream, when applied frequently, significantly reduces the healing time of recurrent herpes labialis lesions. Additionally, it is perceived by the study subjects to reduce itching of the lesions and to have a beneficial overall effect. (J Am Acad Dermatol 1999;41:996-1001.)

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There are an estimated 100 million episodes of recurrent herpes labialis in the United States annually in immunocompetent individuals. Most episodes of herpes labialis pose no major health threat to affected individuals but can be painful, cosmetically unsightly, and, in some patients, induce the fear of transmitting herpes simplex virus (HSV). A number of nucleoside analogs, most with in vitro antiviral capabilities, have been proposed as potential treatments for herpes labialis and other types of herpesvirus infections. In general, the nucleoside analogs, which inhibit herpesvirus DNA polymerase, have not shown promise in the development of an effective topical treatment of recurrent HSV infection. Only one prescription topical treatment, penciclovir (Denavir, SmithKline Beecham, Philadelphia, Pa), has been approved for use in humans in the United States for the treatment of recurrent herpes labialis. The mean duration of lesions was 0.7 days shorter in the subjects treated with penciclovir (n = 732) compared with subjects treated with the vehicle control (n = 734).

A number of studies have been conducted with topical preparations of acyclovir for the treatment of herpes labialis. However, the overall results from these studies have proved to be disappointing. Topical acyclovir is not approved in the United States for use on cold sores and fever blisters in the immunocompetent host. The problems associated with the topical use of acyclovir revolve around inadequate drug delivery in different vehicles, the necessity to begin treatment within the first 12 hours in the course of the outbreak, and low numbers of evaluable patients in the reported studies.

Oral acyclovir is indicated for treatment of first episode genital HSV infections and for long-term suppressive treatment of recurring genital herpes infection in immunocompetent patients with frequent recurrences, that is, 6 or more episodes per year, and for suppression of herpes simplex in immunocompromised patients. Although commonly prescribed, it is not indicated for treatment of individual episodes of recurring genital herpes or for herpes labialis. It is, however, effective as a long-term suppressive agent in individuals with very frequent episodes.

As an alternative to acyclovir and other nucleoside analogues, we investigated the ability of tetracaine, a local anesthetic, to treat the lesions of herpes labialis. Formulations containing up to 2% tetracaine equivalent are approved for over-the-counter (OTC) human use for the relief of pain and itch associated with cold sores and fever blisters. The anticipation that tetracaine would reduce time to healing was suggested by preliminary in vitro observations by one of us (H. G. H.), demonstrating that tetracaine hydrochloride was able to inhibit the replication of HSV. Results from in vitro testing of tetracaine hydrochloride added after infection were confirmed by an independent laboratory. This test consisted of infecting human fibroblast cells in culture with HSV. Supernatant fluids were then collected 24 hours after infection and tested for their ability to form plaques on monkey kidney cells. In this viral yield assay tetracaine hydrochloride was able to inhibit the replication of HSV, whereas lidocaine hydrochloride at a 10-fold greater concentration demonstrated no inhibition (personal communication, S. Chatterjee, University of Alabama at Birmingham). These in vitro results suggested that an OTC topical cold sore preparation containing tetracaine would be superior to currently available topical anesthetics for this indication.

In this study we report the results of a double-blind, placebo-controlled trial in which a topically applied 1.8% tetracaine cream (Viractin) was demonstrated to be effective in reducing the healing time of herpes labialis lesions when compared with placebo.

**PATIENTS AND METHODS**

**Study design**

The primary objective of this study was to assess the relative effectiveness of 1.8% tetracaine cream versus placebo in the treatment of herpes labialis in immunocompetent adults. The study medication was a pharmaceutically acceptable cream that contained stearic acid as the dispersed phase and included methylparaben and chloroxylenol as preservatives. The cream had 1.8% tetracaine base, which is equivalent to 2% tetracaine hydrochloride, as the active ingredient. Sodium lauryl sulfate 1% was included in the active preparation, but was not included in the placebo preparation because of compounding constraints. The tetracaine cream formulation used in this study is commercially available as the OTC cold sore product Cepacol Viractin Cream. The study was randomized, double blinded, and placebo controlled. Eligible patients were at least 18 years of age and had the prodromal symptomatology or lesions of recurring herpes labialis. Patients in whom lesions had been present for more than 48 hours before initiation of study medication were not eligible for enrollment. Written patient informed consent was obtained. A medical history, lesion examination, HSV culture of the lesion, blood chemistry, complete blood cell count, and urinalysis were performed on the day of enrollment, before initiation of medication. Patients were monitored during at least 1 visit during their treatment and during a final visit after healing of their lesions (scab falls off) had occurred.

At enrollment, the patient received a coded tube of medication (either active or placebo, randomized before distribution) and was instructed to self-administer the medication every 2 waking hours until the lesions healed (scab loss), but continued the program only if pain persisted, and over of final day he was patient. This u

**Patient pop**

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**RESULTS**

**Viral cultur**

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(scab loss), but for no more than 12 days. Patients self-evaluated the progress of their treatment by completing a daily record form for healing, relief from itching, relief from pain, and overall benefit. The critical objective parameter of final day healing (scab falls off) was recorded by the patient. This triggered a final visit to the investigator.

**Patient population and evaluation**

A total of 72 patients were enrolled from 4 study centers in the southeastern United States. All patients were 18 years of age or older and had a history of recurring herpes labialis. Patients were entered into the study only if they had prodromal symptoms or clinical signs of herpes labialis in which the lesion had been present for less than 48 hours before institution of medication. Each patient recorded daily observations of (1) time to scab formation, (2) time to healing (scab falls off), (3) degree of itching, (4) degree of pain, and (5) overall perceived benefit. Results from the placebo and active groups were analyzed for statistical significance (P < .05) by the Mann-Whitney test (one-tailed) and the Student t test (one-tailed).

**RESULTS**

**Viral cultures**

All patients had confirmed history of recurrent herpes labialis. Of the 72 patients, 61 (84.7%) tested positive for HSV by viral culture taken at the time of enrollment. A negative viral culture in itself did not exclude a patient from participating in this study. When patients with negative viral cultures were excluded, it did not significantly alter the results.

**Time to scab formation and healing (scab falls off)**

Table I gives the results of the major objective evaluation parameters of this study: time to scab formation and time to healing. There was no difference in the time to scab formation between patients treated with the placebo and those with tetracaine cream. However, there was a statistically significant difference in healing time in patients treated with tetracaine cream compared with patients treated with placebo. Patients treated with active medication healed in an average of 5.1 days compared with 7.2 days for placebo (P = .0002). This represents a 29% reduction in healing time.

Fig 1 is a Kaplan-Meier analysis of the distribution of the healing times and graphically shows the difference between the placebo and 2% tetracaine cream relative to the proportion of patients still with scab over the period of treatment. As shown in Fig 1, the active tetracaine hydrochloride treatment clearly shifts the healing of lesions to shorter times.

**Self-evaluation of benefit and relief from itching and pain**

**Benefit.** Table II shows the patients' self-evaluation of the overall benefit of their treatment as determined on the final visit where benefit was ranked on an index score of 1 to 10 (1 = no benefit, 10 = very effective treatment). Patients treated with tetracaine cream ranked the overall benefit of their treatment significantly higher than the placebo-treated group (7.3 vs 5.9; P = .0359), which indicates that the active medication group had a better subjective opinion of the medication than did the placebo-treated group.

**Table I. Time to scab formation and time to heal of tetracaine cream versus placebo in 72 patients (days)**

<table>
<thead>
<tr>
<th></th>
<th>Placebo mean ± SD (No.)</th>
<th>Tetracaine cream mean ± SD (No.)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to scab formation</td>
<td>2.4 ± 0.27 (34)</td>
<td>2.3 ± 0.26 (32)</td>
<td>.4279</td>
</tr>
<tr>
<td>Time to heal</td>
<td>7.2 ± 0.36 (33)</td>
<td>5.1 ± 0.35 (33)</td>
<td>.0002</td>
</tr>
</tbody>
</table>

**Table II. Patient self-evaluation of benefit of treatment: tetracaine cream versus placebo**

<table>
<thead>
<tr>
<th>Treatment benefit (index) (No.)</th>
<th>Placebo mean ± SD (No.)</th>
<th>Tetracaine cream mean ± SD (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment benefit index (No.)</td>
<td>5.9 ± 0.60 (34)</td>
<td>7.3 ± 0.48 (37)</td>
</tr>
<tr>
<td>P = .0359</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table III. Patient daily ranking scales for relief of itching by day and treatment group

<table>
<thead>
<tr>
<th>Day of study</th>
<th>Placebo (No.)</th>
<th>Tetracaine cream (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.1 ± 0.36 (32)</td>
<td>3.7 ± 0.47 (35)</td>
</tr>
<tr>
<td>2*</td>
<td>3.1 ± 0.42 (29)</td>
<td>2.3 ± 0.30 (34)</td>
</tr>
<tr>
<td>3*</td>
<td>2.7 ± 0.36 (31)</td>
<td>2.0 ± 0.26 (35)</td>
</tr>
<tr>
<td>4</td>
<td>2.0 ± 0.26 (29)</td>
<td>1.5 ± 0.16 (32)</td>
</tr>
<tr>
<td>5</td>
<td>1.6 ± 0.22 (29)</td>
<td>1.3 ± 0.12 (33)</td>
</tr>
<tr>
<td>6</td>
<td>1.4 ± 0.18 (29)</td>
<td>1.2 ± 0.07 (35)</td>
</tr>
<tr>
<td>7</td>
<td>1.3 ± 0.14 (25)</td>
<td>1.1 ± 0.06 (30)</td>
</tr>
</tbody>
</table>

Data expressed as mean, standard errors, and sample size.

*Student t test, P < .05, one-tailed.
*Mann-Whitney U test, P < .05, one-tailed.

Analysis of daily rankings of benefit, as shown in Table II, indicate that patients receiving tetracaine cream scored significantly greater benefit from the second day of treatment until the end of therapy when compared with the placebo-treated group.

Relief from itching. Each patient kept a daily record of the ability of their medication to relieve itching, and an index score was calculated for this subjective evaluation (1 = absence of itching; 10 = maximum itching). Table III shows the patients' daily rankings for relief from itching. This data indicates that on days 2 and 3, the active medication provided significantly greater relief from itching when compared with placebo (P < .05). Days 2 and 3 were the most severe periods of itching for the patients. After day 3, itching decreased to minimum levels in both the active and placebo-treated groups.

Relief from pain. Each patient kept a daily record of relief from pain, and a separate index score was calculated for that parameter (1 = no pain at all; 10 = most severe pain imaginable). Table IV shows that pain scoring was in the lowest third of the pain scale for both active and placebo groups. There was not a statistical difference between the active group and the placebo group for pain relief.

Safety
No adverse reactions were observed or reported from either the active or placebo groups.

DISCUSSION
This study was designed to determine the effectiveness and safety of a topical formulation containing 1.8% tetracaine equivalent, in a cream base, for the treatment of herpes labialis. Patients in this protocol self-applied medication and self-evaluated the effects of treatment on a daily basis. The study was double-blinded with a placebo cream containing neither tetracaine nor sodium lauryl sulfate used as a control.

The results of our study indicate that the healing time of herpes labialis lesions treated with topical 1.8% tetracaine equivalent cream was significantly decreased, compared with placebo, with a reduction of nearly 50% to the final day of healing as indicated by scab loss (active = 5.1 days; placebo = 7.2 days). Based on market research, a decrease in healing time is the most important benefit in treating herpes labialis from the patients' point of view (personal communication, J. Soinski). Patients welcome the end of a cosmetically undesirable lesion on the lips or face and the perceived social stigma associated with such lesions.

The results of this study can be contrasted with several studies that reported the results of various regimens of treatment with topical acyclovir. In an initial study by Spruance et al., 5% acyclovir in polyethylene glycol failed to produce significant benefit when compared with a placebo control. A second controlled trial showed that 10% acyclovir also was not effective. In contrast to these initial negative reports, two separate studies have been published that purport to show that 5% acyclovir in a propylene glycol-containing vehicle (not available in the United States) does provide positive clinical benefit in recurrent herpes labialis. Fiddian et al. in 1983 reported the results of a double-blind, placebo-controlled study of 5% acyclovir propylene glycol ointment in 49 patients with recurrent herpes labialis. In this study the median time to healing for the active drug was 4 days compared with the placebo time of 6 days. Fiddian and Ivanyi also reported a positive therapeutic effect for topical acyclovir in a second trial. Van Vloten, Swart, and Pot also in 1983, reported the results of another trial conducted with 5% acyclovir in propylene glycol using 60 episodes from
30 patients with recurrent herpes labialis. Only patients who started therapy within 12 hours after the onset of symptoms were included in the analysis. These authors reported that the mean time in days to complete healing with 5% acyclovir was 5.4 days compared with 6.6 days for the placebo. Additional studies with topical acyclovir23 have demonstrated no significant clinical effect. Other attempts at topical treatment of herpes labialis with other known anti-herpes agents have also produced equivocal results.15-18

The 2-day reduction time to healing for the 1.8% tetracaine equivalent cream tested in this study compares favorably with the 1- to 2-day reduction in healing time found for the European 5% acyclovir cream formulation and to the half-day shortening reported for the prescription penciclovir cream. As noted above, the 5% acyclovir ointment prescription product available in the United States has never been shown to significantly reduce time to healing for herpes labialis lesions. In considering the efficacy of topical tetracaine treatment, certain aspects of this study design should be emphasized. Because the treatment of lesions in this study was initiated by the investigator upon enrollment, the reduction in healing time seen with the active medication was additionally significant. In this study, the majority of patients did not start treatment until sometime between 24 and 48 hours after the appearance of the lesion, a time at which the infection was well on its way to full lesion development. These are not ideal treatment conditions. It is likely that under conditions of actual usage of this medication patients would self-initiate treatment early during the first 24 hours of the recurrent outbreak. Under those circumstances, it is possible patients would experience an even greater reduction in healing time than that seen in this study.

Although subjective end points such as perceived benefit, degree of pain, and degree of itching are difficult to scientifically analyze, it is important in the treatment of diseases such as herpes labialis to gain an understanding of the patients’ perception of the benefits of the treatment. In this study the patients graded the overall benefit of the active medication at a significantly greater score than placebo. This became apparent on day 3 and continued until healing was complete.

Likewise, when patients evaluated their own itching symptoms on a daily basis, the group treated with 1.8% tetracaine equivalent cream showed significant improvement on days 2 and 3 compared with the placebo group. Days 2 and 3 were the days of most intense itching. This is an expected finding because itching is an epidermal symptom and tetracaine is known to be effective as a topical anesthetic. Although itching was significantly reduced, the reduction of pain was not significantly different between the active and placebo groups. Because tetracaine is an accepted topical anesthetic, this finding is presumed to be a result of the enrollment criteria for the study. Note that patients were enrolled up to 48 hours after lesion formation. Because pain is more intense in the earliest lesion stages, a significant portion of the enrolled patients began the study with lesions that had progressed past being painful. This explanation is supported by the pain scores, which show that pain was not a major patient complaint in either group. Patient scoring of pain in both the active and the placebo groups was highest at the day of enrollment and never exceeded a value of 3.8 on a scale of 1 to 10 with 1 representing “no pain at all.”

The mechanism of action of tetracaine in this study is unknown. Tetracaine and related compounds have been shown to have a number of potential actions on cells and cellular membranes and can act as reversible membrane perturbers. It can be speculated that tetracaine might directly affect the synthesis of HSV glycoprotein membrane synthesis or morphogenesis. Experiments to test this hypothesis and to confirm and extend the preliminary findings of the ability of tetracaine to inhibit the replication of HSV in vitro would be required to establish a mechanism.

In summary, a 1.8% tetracaine equivalent cream was found to be safe and effective for reducing the healing time of recurrent herpes labialis lesions and for reducing itching associated with this disease. These positive findings suggest that tetracaine at concentrations acceptable for OTC use is an effective medication for treatment of herpes labialis and should be further investigated in expanded clinical trials involving both genital and oral herpes.

REFERENCES

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